Leukoencephalopathy after prophylactic whole-brain irradiation with or without hippocampal sparing: a longitudinal magnetic resonance imaging analysis

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Abstract: PURPOSE Neurocognitive changes are well described after prophylactic or therapeutic whole-brain radiotherapy (WBRT) and have been reported as early as 3 months after radiotherapy (RT). Therefore, WBRT with protection of the hippocampal region (hippocampal avoidance, HA) has been proposed to preserve neurocognition. Our aim was to compare the risk of leukoencephalopathy after prophylactic cranial irradiation (PCI) with or without HA. METHODS Patients with small-cell lung cancer who received either lateral-opposed field PCI (non-HA-PCI; n = 9) or hippocampus avoidance PCI (HA-PCI; n = 9) with available magnetic resonance imaging (MRI) follow-up were identified and age matched. Pre-therapeutic and follow-up MRI after RT was analysed for leukoencephalopathy based on the Fazekas score. Bilateral cortical and subcortical brain structures were segmented and analysed for alterations in dosimetric parameters and volumes. RESULTS There was no significant difference of Fazekas scores between groups at baseline. Fazekas score differed in post-treatment with a median of 1 in the HA-PCI group and 2 in the non-HA-PCI group (p = 0.007). Significant increase of Fazekas score over time after RT was observed for HA-PCI patients (p = 0.001) but not for non-HA-PCI patients. Dmax (highest radiation dose) and brain volume receiving doses >25Gy were higher in HA-PCI patients. There were no significant volumetric differences for segmented brain structures between groups. CONCLUSION Radiological changes are more prominent after HA-PCI than after non-HA-PCI. Although no standardised neurocognitive testing was performed, the significantly increased Fazekas scores after HA-PCI are expected to interfere with neurocognitive function. Prospective long-term neurocognitive studies are warranted before HA-PCI is implemented in routine clinical practice.

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Leukencephalopathy after prophylactic whole brain irradiation with or without hippocampal sparing: a longitudinal MRI analysis

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Abstract

Purpose

Neurocognitive changes are well described after prophylactic or therapeutic whole brain radiotherapy (WBRT) and have been reported as early as 3 months post RT. Therefore WBRT with protection of the hippocampal region (hippocampal avoidance, HA) has been proposed to preserve neurocognition. Our aim was to compare the risk of leukencephalopathy after prophylactic cranial irradiation (PCI) with or without HA.

Methods

Patients with small cell lung cancer who received either lateral-opposed field PCI (non-HA-PCI; n=9) or hippocampus avoidance PCI (HA-PCI; n=9) with available MRI follow-up were identified and age matched. Pre-therapeutic and follow-up MRI after RT were analyzed for leukencephalopathy based on the Fazekas score. Bilateral cortical and subcortical brain structures were segmented and analyzed for alterations in dosimetric parameters and volumes.

Results

There was no significant difference of Fazekas scores between groups at baseline. Fazekas score differed in post-treatment with a median of 1 in the HA-PCI group and 2 in the non-HA-PCI group (p=0.007). Significant increase of Fazekas score over time after RT was observed for HA-PCI patients (p=0.001), but not in the non-HA-PCI patients. Dmax (highest radiation dose) and brain volume receiving doses >25Gy were higher in HA-PCI patients. There were no significant volumetric differences for segmented brain structures between groups.

Conclusion

Radiological changes are more prominent after HA-PCI than after non-HA-PCI. Although no standardized neurocognitive testing was performed, the significantly increased Fazekas scores after HA-PCI are expected to interfere with neurocognitive function. Prospective long-term neurocognitive studies are warranted before HA-PCI is implemented in routine clinical practice.

Introduction

Prophylactic cranial irradiation (PCI) is the standard of care in limited and extensive stage small cell lung cancer (SCLC), a disease with a high propensity of metastatic spread to the brain. PCI reduces the occurrence of brain metastases and increases overall survival (OS) (Aupérin et al. 1999; Slotman et al. 2007), although this has been challenged recently by a Japanese trial for extensive disease SCLC (Takahashi et al. 2017). Nevertheless, this OS advantage comes at a price.

Irradiation of the brain is associated with a dose-dependent induction of leukencephalopathy described already very early in the history of WBRT (Sheline, Wara, and Smith 1980). Patients affected by leukencephalopathy may develop some degree cognitive deficits affecting key brain functions such as memory, executive function, attention and concentration as well as learning disorders, dementia and gait disturbances(Bompaire et al. 2018; Soussain et al. 2009). The pathophysiology mediating this syndrome is thought to involve demyelination, vascular compromise, and direct damage to neurons.

Apart from leukencephalopathy, hippocampal neural stem-cell injury during WBRT is assumed to play a crucial role for memory decline. Therefore, intensity-modulated radiotherapy (IMRT) and volumetric modulated radiotherapy (VMAT) were implemented to avoid the hippocampal neural stem-cell compartment during WBRT (hippocampal avoidance whole-brain irradiation, HA-WBRT).

Whether this approach actually reduces the occurrence of radiation-induced leukencephalopathy or potentially even exacerbates this process through dose maxima in the areas surrounding the hippocampus remains unclear.

To address this question, we compared brain MRI scans of patients treated with hippocampus avoidance PCI (HA-PCI) after its introduction in 2015 in our department to patients' MRI scans treated earlier with regular PCI without HA (non-HA-PCI) for the occurrence and severity of leukencephalopathy.

Material and methods

Patient cohort:

All SCLC patients treated with PCI at our institution from 2013 to 2018 (n= 40) were identified using Eclipse Data query (Varian Inc, Palo Alto, CA, USA). Only patients with MRI at baseline and at least one follow-up MRI were selected for final analyses, leaving 9 patients without and 17 patients with HA-PCI for the overall analyses for leukencephalopathy scoring (**Table 1**). To account for confounding HA-PCI and non-HA-PCI patients were separately analysed after matching based on age, leaving nine patients in each group.

HA-PCI was introduced in our institution in 2015, while non-HA-PCI was applied from 2011 to 2015. Patients' characteristics were evaluated, including ECOG, tumor stage and regimen of initial chemotherapy from the institutional database. The study was approved by the Local Ethics Commission of the Medial Faculty of the University of Zurich, University Hospital Zurich (BASEC-Nr. 2018-01794).

Treatment and volume delineation:

For all patients treated with HA-PCI, hippocampal contouring required a three-dimensional spoiled gradient echo: a magnetization-prepared rapid gradient echo axial MRI scan of the brain with an axial slice thickness ≤ 1.5 mm, fused to a RT-planning head computed tomography (CT) scan with an axial slice thickness ≤ 2.0 mm. Bilateral hippocampal contours were manually delineated, based on the Contouring Atlas for RTOG 0933 on the fused MRI-CT image set and expanded by 5 mm to generate HA regions(Hippocampal Contouring: A Contouring Atlas for RTOG 2016). Clinical target volume (CTV) was defined as the whole brain parenchyma. The planning target volume (PTV) was defined as the CTV excluding the HA regions plus a 3 mm isotropic margin. Dose prescription for prohpylactic cranial irradiation was 10 times 2.5 Gy. All plans were normalized to 92 % of the PTV covered by 25 Gy. The minimal dose to the hippocampus, defined as D100% of the hippocampus, was not allowed to exceed 9 Gy, and the maximum hippocampal dose was not being allowed to exceed 16 Gy; D100% of the hippocampus exceeding 10 Gy and maximum hippocampal doses exceeding 17 Gy were

considered as unacceptable deviations and required re-planning before treatment initiation (Gondi et al. 2014).

For HA planning purposes automated treatment planning module, AutoPlanning (AP), included in Pinnacle 14.0 (Philips Radiation Oncology Systems, Fitchburg, WI) was used for plan optimization. The model used for optimization was developed to provide an improved dose distribution within the PTV with significantly reduced Dmax (Krayenbuehl et al. 2017) and has been adapted for a dose fractionation of 10 x 2.5 Gy instead of 10 x 3 Gy. Only the constraints on the PTV were changed, beam geometry and organ at risk objectives remained unchanged.

For the non-HA-PCI group lateral opposed fields were used with individual Multileaf collimation MLC shielding adapted to the PTV Plans were normalized to a dose point located in the PTV. The dose point had to be set in such a way that 95% of the PTV had to be covered by at least 95% and the maximal point dose had to be kept below 110% of the prescribed dose. However, for non-HA-PCI no constraints were set for avoiding the hippocampal regions.

Leukencephalopathy scoring

Pre-therapeutic MRI and regular follow-up MRI starting on average 7 months (±6) after RT were analyzed. Based on the Fazekas classification, the degree of leukencephalopathy was scored on T2-FLAIR MRIs in all patients independently and blinded by one neuroradiologist (XX) and two radiation oncologists (YY, ZZ); where the three physicians disagreed a consensus was reached (Fazekas et al. 1987).

Leukencephalopathy or its radiological correlate in forms of white matter hyperintensities or white matter lesions can be divided into periventricular and deep white matter lesions. The distinction is made on base of visual rating scales, whereas histopathology and aetiology between these two classes seems to be different (K. W. Kim, MacFall, and Payne 2008; Debette and Markus 2010). We focused on periventricular white matter hyperintensity as high periventricular white matter lesion load is the predominantly observed pattern of white matter change after WBRT and may be associated with reduced cognitive function (Griffanti et al. 2018; Monaco et al. 2013). Periventricular Fazekas classification describes the different types of hyperintense signal abnormalities surrounding the ventricles. Periventricular hyperintensity (PVH) was rated as 0 = absence, 1 = “caps” or pencil-thin lining, 2 = smooth “halo,” 3 = irregular PVH extending into the deep white matter. It relates to a combination of demyelination, and subependymal gliosis, as well as small vessel ischemia (K. W. Kim, MacFall, and Payne 2008; Wardlaw, Valdés Hernández, and Muñoz-Maniega 2015).

Analysis of RT dose-volume relations

Dose volume histograms (DVHs) were exported in text format using Eclipse Treatment Planning System (Version 13.0, VARIAN, Palo Alto, USA), imported into R (Version 3.3.2., R Foundation for Statistical Computing, Vienna, Austria) and processed using DVH metrics library (https:// cran.r-project.org/web/packages/DVHmetrics/index.html) to generate dose volumes and dose volume histograms. DVH metrics were further analyzed using a paired Wilcoxon rank-sum test for statistical testing (GraphPad Prism version 6.00, GraphPad Software, San Diego, California, USA). Dosimetric parameters for brain parenchyma, including Dmax, Dmean, V26 Gy and V25 Gy, were analyzed. A p-value below 0.05 was considered as statistically significant.

Analysis of volumetric alterations

The scanning protocol included a T1-weighted 3D magnetization rapid-acquisition gradient echo (MP-RAGE) acquired in an axial orientation. MRI data sets were examined for image quality. The T1-weighted images were transformed from the DICOM to NRRD file format by creating a nhdr header file for each subject. Cortical thickness analysis was performed using FreeSurfer version 5.3 (Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA). Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/)(B. Fischl, Sereno, and Dale 1999; Bruce Fischl et al. 1999). The images were aligned to a common atlas and grayscale intensity was normalized and corrected for inhomogeneity of the magnetic field. All voxels were labeled as gray matter, white matter or cerebral spinal fluid and the gray matter surface (pial) and white matter surface were created. The deep grey matter in each hemisphere was segmented into seven subcortical structures: caudate nucleus (CN), putamen (PT), globus pallidus (GP), thalamus (TH), hippocampus, amygdala and nucleus accumbens. For each subcortical structure the respective volume was calculated. Cortical surfaces were parcellated into discrete units based on gyral and sulcal anatomy. All processed images were visually inspected for topological defects, geometric inaccuracies due to brain lesions and other defects. A list of structures analyzed with significant volumetric differences is provided in **Table 2** and an example figure of analyzed areas in **Figure 1**. Bonferroni correction was applied to correct for multiple testing.

Results

Patient characteristics are depicted in **Table 1**. The median age of participants in the non-HA-PCI group was 57 (±5) years and 68 (±7) years in the matched HA-PCI group (p = 0.3). Overall, median age of all 17 HA-PCI patients was 70 (±8) years. Median MRI follow up was 7 months in all groups. Age matching was performed to control for age as a potential confounding factor for the development for leukencephalopathy.

There was no significant difference in Fazekas score between groups prior to RT (p = 0.28 **Figure 2**). The median change of Fazekas score from pre to post treatment was 0 (mean: 0.2) for the non-HA-PCI group and 1 (mean: 1.1) for the HA-PCI group (p = 0.002; **Figures 2, 3**).

The Fazekas score differed between the two groups at first follow-up (median: 6 months post treatment): in the HA-PCI group, the median value of the Fazekas score was 2 versus 1 in the non-HA-PCI group (p = 0.007). Furthermore, a significant increase of the Fazekas score at follow-up MRI after RT was observed in the HA group comparing pre- and post-treatment MRIs (p = 0.001). There was no significant difference comparing pre- and post-treatment MRIs in patients treated with non-HA-PCI.

Significant differences amongst dosimetric parameters and hippocampal/cerebellar volumes are listed in **Table 3.** Details for all volumetric parameters are provided in the supplementary appendix. Median Dmax was higher in the HA-PCI compared to the non-HA-PCI group (28.2 Gy ± 0.4 vs. 27.0 Gy ± 1.5; p = 0.002). V26 Gy also showed higher values in the HA-PCI compared to the non-HA-PCI group (12.2 % ± 38.2 vs. 2.7 % ± 4.9; p = 0.03). There were no significant differences in volumetric parameters between PCI and HA-PCI groups.

Discussion

This study reports increased leukencephalopathy after HA-PCI compared to non-HA-PCI during follow-up: in the HA group, the median value of the Fazekas classification amounted to 2 (range 1-3) versus 1 (range 1-2) in the non-HA-PCI group (Figure 3). The significant increase of the Fazekas classification from pre- to post treatment MRIs reported in this study represents the first evidence of a greater risk of leukencephalopathy after HA-PCI compared to non-HA-PCI. There were no significant volumetric differences for segmented brain structures between groups.

Previous reports have shown increased leukencephalopathy after whole brain irradiation either in a prophylactic or a definitive intention (Frytak et al. 1989; Monaco et al. 2013). Corn et al. described a dose-dependence of leukencephalopathy after WBRT (Corn et al. 1994). In our study, HA-PCI patients received a significantly higher V26/V25 Gy with increased dose maxima compared to conventionally treated PCI patients in the white matter (**Table 3**). This is also reported in studies with therapeutic HA-WBRT: sparing of the hippocampi comes at the cost of higher mean and maximum brain doses (Gondi et al. 2014).Similar imaging changes in white matter have been linked to neurocognitive dysfunction and decline in several neurocognitive disorders (Fazekas et al. 1987; O'Sullivan et al. 2001; Kondziolka et al. 2005). Moreover, periventricular white matter hyperintensity seems to play an more important role with regard to neurocognition decline than deep white matter hyperintensity does (Griffanti et al. 2018). In an MRI study periventricular white matter hyperintensities volume paralleled the decline in mental processing speed, whilst neither presence nor progression of deep white matter hyperintensity was associated with changes in any of the used cognitive tests (van den Heuvel et al. 2006). Therefore, we consider these observed changes clinically significant, although our patients were not tested for neurocognitive function.

To date, radiation to the whole brain is still the guideline recommended treatment modality in prophylactic intention for limited and extensive disease SCLC or the definitive treatment in the presence of multiple brain metastases of all cancer types (NCCN Guidelines for Small Cell Lung Cancer 2017; Brown et al. 2018).

However, neurocognitive impairment mainly measured at 4 months post-RT is of concern and several possibilities for preservation of neurocognition have been investigated. Gondi et al. found that HA-WBRT is associated with significant memory preservation compared with a prespecified historical control (Gondi et al. 2014). Brown et al. found that memantine reduces the rate of decline in memory, executive function, and processing speed after WBRT (Brown et al. 2013). Therefore, the introduction of HA-WBRT, as well as the use of concomitant

memantine are considered possible options to prevent or at least alleviate these neurocognitive changes. As there is a low risk of hippocampal failures, HA-WBRT appears to be safe (Gondi et al. 2010). Redmond et al. suggest a potential benefit of HA in limiting the neuropsychological sequelae of brain radiation, but with a risk of failures in the spared region (Redmond et al. 2017).

The RTOG-0933 was the first prospective evidence that HA-WBRT leads to significant preservation of neurocognition (Gondi et al. 2014). Recently, the prospective randomized NRG Oncology CC001 study confirmed that conformal avoidance of the hippocampal neuroregenerative stem cell niche during WBRT preserves neurocognitive function while achieving similar intracranial control and survival.

In contrast, we observed that, despite significantly improved homogenized dose distributions with considerably fewer high dose areas compared to the planning guidelines of RTOG-0933, patients with HA- PCI developed leukencephalopathy strikingly more frequently and more pronounced as detected by serial follow-up cMRI than patients receiving lateral-opposed field PCI.

Several trials on HA-PCI are currently conducted (listed in **Table 4**). Despite the encouraging results, long-term outcome of HA-WBRT has not been studied so far and one concern is that cortical dose – which is higher in HA-WBRT - may be more relevant for long-term neurocognitive functioning. This concern was corroborated in light of the results of NCT01780675 presented at ESTRO 2019. In the not yet fully published study Belberdos et al. investigated hippocampus-dependent memory functioning and safety after PCI with or without hippocampus sparing in SCLC patients (Belderbos et al. 2019). This randomized study recruited 168 patients and neurocognitive testing included the Hopkins Verbal Learning Test-Revised (HVLT-R). Neurocognitive functioning was assessed at 6 different time points until 24 months after irradiation. A neurocognitive decline was observed after treatment. However, without a significant difference between the two arms. Furthermore, the incidence of brain recurrences was not increased in the hippocampus avoidance region, whilst this issue was of great concern and debate after retrospective series showed such an increase in their cohorts (Korkmaz Kirakli and Oztekin 2017). Recurrence rates generally vary and are lower than 5% in the hippocampus regions (Y. Kim et al. 2019; Sun et al. 2016). We did not observe higher recurrence rates in our data, but this was not quantified as this was not the purpose of our study.

The findings of our study urgently need to be validated in independent patient cohorts, ideally from prospective trials, and correlated with neurocognitive function tests, as HA-WBRT and

HA-PCI are already being implemented into clinical routine after the positive results of RTOG-0933 and 0614 for the early neuro-cognitive endpoints.

Whether this leads to a better preservation of neurocognitive function or might even be associated with an increased risk of late side effects should be further investigated in longitudinal studies. Our results also suggest that the dose response for white matter changes may be very steep, as we already employed an automated HA-PCI planning technique implementing harder constraints for the maximally allowed brain dose compared to the RTOG-0933 planning criteria and still saw these significant changes for PCI patients receiving brain doses of less than 30 Gy.

Limitations of this study include its retrospective nature and the small sample size, particularly for the non-HA PCI group. This study did also not incorporate covariates such as use of chemotherapy in the analysis; still, both groups received similar regimens and no difference in the use of chemotherapy was observed. However, this study's strength is that pre- and post-treatment MRI scans were available: regular MRI follow-up is not standard of care, but has been implemented in our institution.

Conclusion

Although the RTOG 0933 trial reported preservation of short-term neurocognitive function by HA-WBRT, our results suggest that long-term radiological changes are more pronounced after HA-PCI than after non-HA-PCI. While no neurocognitive testing was performed in our patients, the increased Fazekas score after HA-WBRT is indicative of potential negative long-term effects. Long-term neurocognitive investigation from prospective studies should be performed before HA-PCI is implemented in routine clinical practice.

Figure legend:

Figure 1: An example of the segmented structures

Figure 2: Fazekas score for the individual subjects in the non-HA-PCI and HA-PCI groups at first follow-up and pre-treatment.

Figure 3: Average Fazekas score for the non-HA-PCI and HA-PCI groups at follow up post treatment with the error bars representing the mean and +/- standard deviation.
□= Matched Patients; □ = unmatched patients

Figure 4: T2-Flair of a patient prior HA-PCI (1/2A) and after (1/2B) and to the brain. 2A shows a different patient with non-HA-PCI prior (3/4A) and post (3/4B) treatment.

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Figure 1:

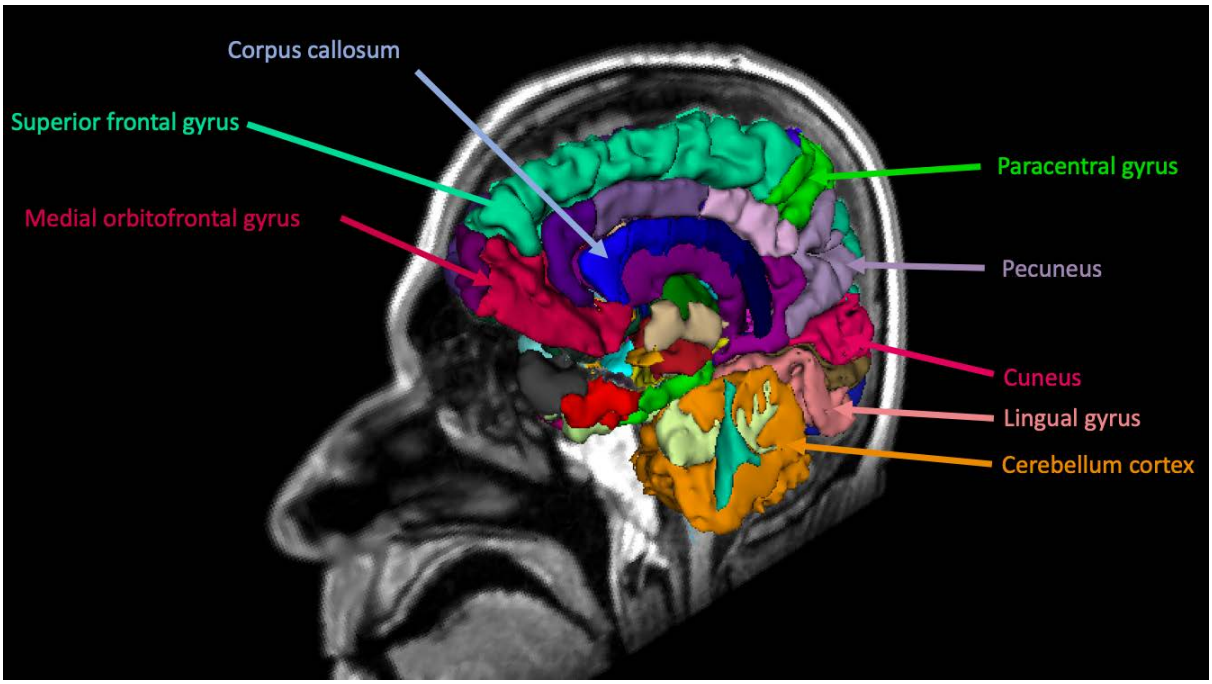
Corpus callosum
Superior frontal gyrus
Medial orbitofrontal gyrus
Paracentral gyrus
Pecuneus
Cuneus
Lingual gyrus
Cerebellum cortex

Figure 2:

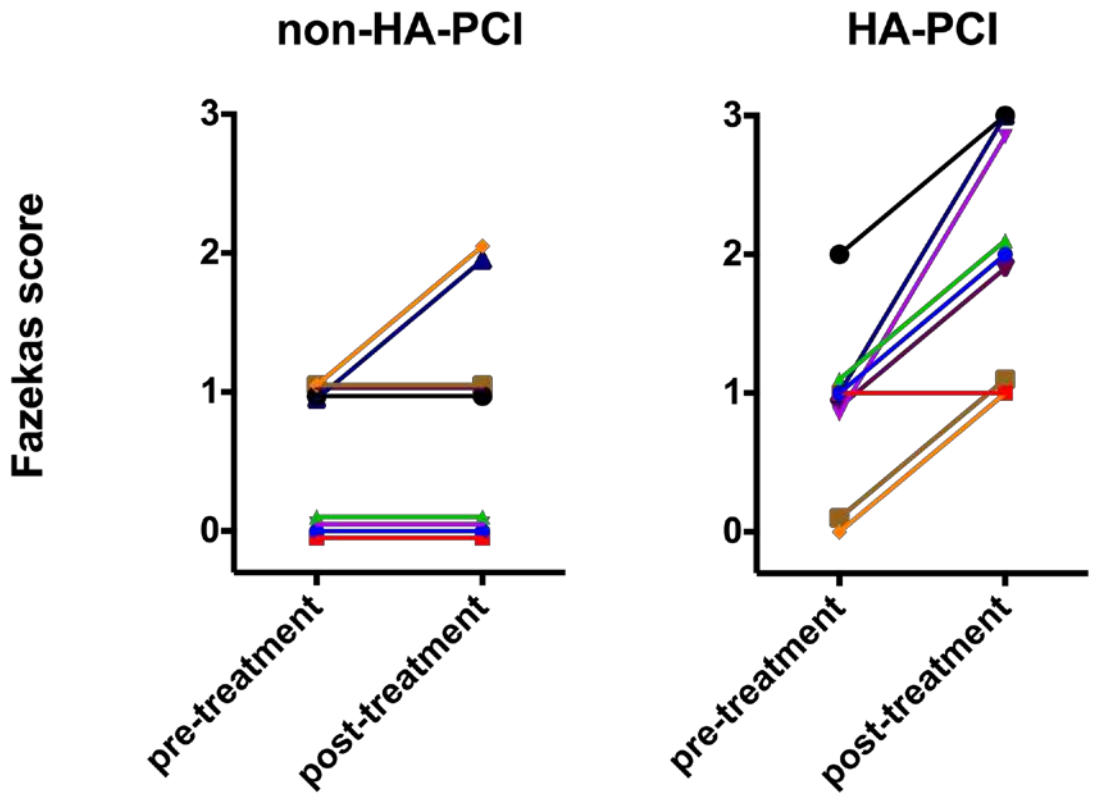

Figure 3:

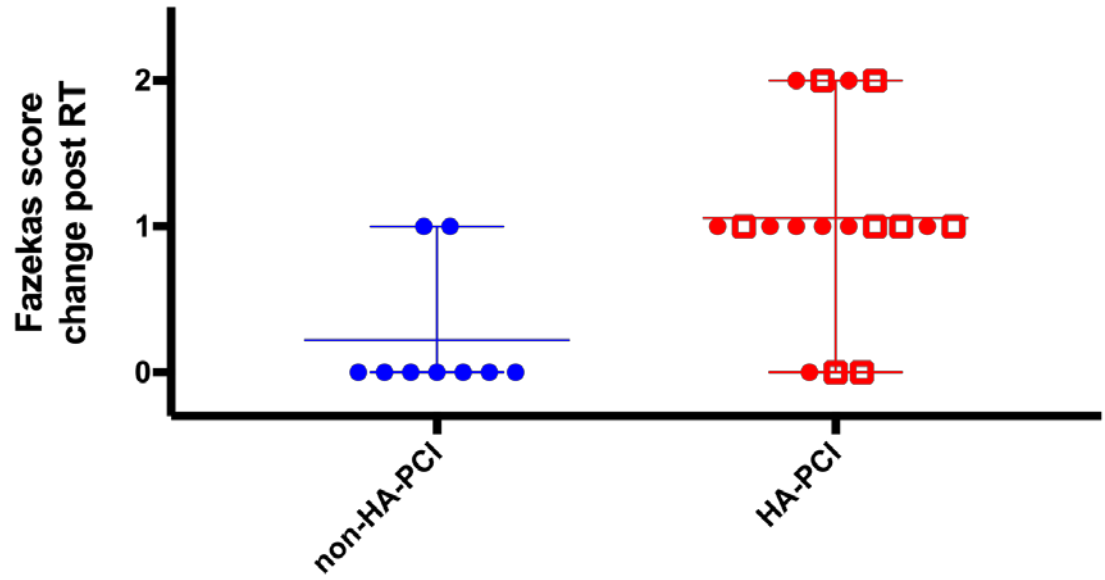

Figure 4:

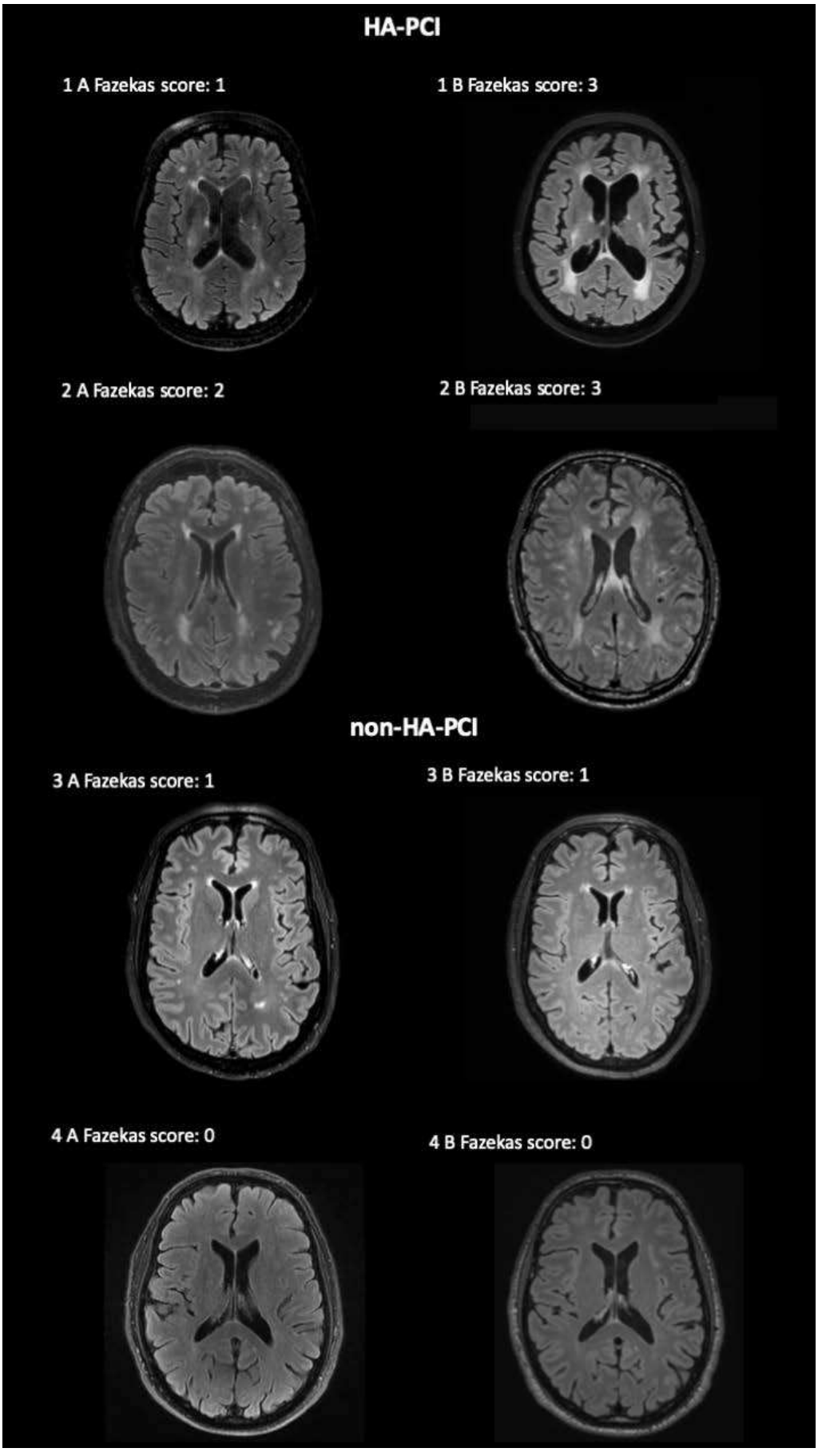
HA-PCI
1 A Fazekas score: 1
1 B Fazekas score: 3
2 A Fazekas score: 2
2 B Fazekas score: 3
non-HA-PCI
3 A Fazekas score: 1
3 B Fazekas score: 1
4 A Fazekas score: 0
4 B Fazekas score: 0

Table 1 Patient characteristics.

	Prophylactic cranial irradiation (age matched)	Hippocampal avoidance Prophylactic cranial irradiation (all)	Hippocampal avoidance Prophylactic cranial irradiation (age matched)
Number	n = 9	N = 17	n = 9
median Age (range)	57 years (54 – 69)	70 years (51–84)	64 years (51–71)
Sex			
Male	7	12	6
Female	2	5	3
ECOG			
0-1	3	15	7
2	6	2	2
Disease Stage			
Limited	5	5	3
Extensive	4	12	6
Response to initial chemotherapy			
complete	2	2	2
partial	7	14	7
minor	0	1	0
Total number of cycles of initial chemotherapy			
one	0	1	0
three	0	1	0
four	5	6	4
five	0	2	2
six	4	7	3
Regimen of initial chemotherapy			
Carboplatin / Etoposide	5	11	5
Cisplatin / Etoposide	4	5	4
median MRI follow-up in month (range)	7 (2 – 14)	7 (2 – 11)	7 (2 – 11)

Table 2: Volumes of segmented cerebral structures (in mm^3)

Cerebral structure	No HC	HCS	p-value
Left - Lateral - Ventricle	13454.3 (±14453.4)	18467.4 (±8351.8)	0.94
Left - Inf - Lateral - Ventricle	453.5 (±682.1)	922.2 (±366.3)	0.31
Left - Cerebellum - WM	12478.9 (±2754.6)	13542.8 (±3657.7)	0.44
Left - Cerebellum - Cortex	51047.4 (±6465.8)	48690.8 (±4425.0)	0.65
Left - Caudate	2847 (±789.1)	3089.3 (±387.2)	0.81
Left - Putamen	4368.2 (±694.4)	3885.2 (±596.8)	0.56
Left - Pallidum	1758 (±246.1)	1744 (±289.9)	0.28
3rd - Ventricle	1555.3 (±814.0)	2097.8 (±521.4)	0.19
Brain - Stem	19498.7 (±4052.0)	20382.1 (±1753.0)	0.73
Left - Hippocampus	3802.9 (±395.7)	3913.9 (±352.4)	0.18
Left - Amygdala	1445.8 (±299.7)	1398.3 (±58.9)	0.69
CSF	1156.3 (±913.0)	1100.2 (±193.2)	0.29
Left - Accumbens - area	380.3 (±102.6)	398.4 (±117.2)	0.93
Left - Ventral DC	4294.7 (±621.1)	4137 (±382.3	0.97
Left - choroid - plexus	854.5 (±359.5)	818 (±260.5)	0.40
Right - Lateral - Ventricle	11840.6 (±14863.7)	14012 (±5724.3)	0.63
Right – Inf – Lateral - Ventricle	692.7 (±432.7)	817.9 (±550.4)	0.31
Right - Cerebellum - WM	14566.1 (±3264.2)	12753.9 (±2802.0)	0.35

Right - Cerebellum - Cortex	52821.2 (±6460.2)	49448 (±3166.9)	0.34
Right - Thalamus	6780.1 (±965.0)	6595.1 (±838.8)	0.30
Right - Caudate	3333.3 (±744.3)	3246.6 (±338.5)	0.38
Right - Pallidum	1579.9 (±271.7)	1735.6 (±305.2)	0.88
Right - Accumbens - area	428.9 (±109.9)	398.6 (±65.3)	0.41
Right - Ventral DC	4073.2 (±680.4)	4105 (±351.9)	0.91
Right -Hippocampus	4001.5 (±485.1)	41338 (±509.2)	0.54
Optic - Chiasm	226.9 (±91.4)	247.3 (±67.0)	0.71
CC_Posterior	971 (±429.4)	897.9 (±207.2)	0.07
CC_Mid_Anterior	514 (±128.0)	476.4 (±110.1)	0.66
CC_Anterior	857.6 (±250.5)	829.8 (±196.0)	0.13

CC - corpus callosum; CSF - cerebrospinal fluid; DC - diencephalon; Inf - inferior; WM - white matter

Table 3 Differences amongst total brain dose and volumetric parameters.

Median Doses total brain	non-HA-PCI	HA-PCI	p-value
Dmax	26.5 Gy (± 1.5)	28.2 Gy (± 0.4)	0.002
Dmean	25.0 Gy (± 0.8)	25.0 Gy (± 0.3)	0.11
V26 Gy	2.2 % (± 4.9)	12.2 % (± 38.2)	0.03
V25 Gy	47.3 % (± 21.4)	68.5 % (± 17.5)	0.02
Cortical structure volumes			
Left - Hippocampus	3802,9 (±395,7)	3913,9 (±352,4)	0.456
Right -Hippocampus	4001.5 (±485.1)	41338 (±509.2)	0.51
Left Cerebellum	63526.3 (±9220.4)	62233.6 (±8082.7)	0.54
Right Cerebellum	67387.3 (±9724.2)	62201.9 (±5968.9)	0.35

Table 4: Trials on HA-PCI currently conducted:

Trial	PI	Projected Participants	Arms/Intervention	Primary Endpoint	Secondary Endpoint	Status
NCT02635009	Vinai Gondi NRG Oncology	304	Prophylactic Cranial Irradiation 3D RT vs Hippocampal Avoidance PCIusing IMRT 10 times 2.5 Gy (total 25 Gy)	HVLT-R delayed recall deterioration status, defined using the Reliable Change Index (RCI) and Intracranial relapse rate	Cost-effectiveness, Adverse Events, Intracranial relapse rate, OS, HRQoL, Preservation of neurocognitive function, Time to neurocognitive failure	Recruiting
NCT01797159	Kristin Redmond, M.D. Johns Hopkins University	125	Hippocampal sparing PCI in SCLC	Performance on the HVLT-R at 6 month in comparison to historical control group (RTOG 0212)	HVLT-R at 12 month in comparison to historical control group (RTOG 0212), cognitive function, QoL, HC brain metastasis, leptomeningeal carcinomatosis, survival rates	Active, not recruiting
NCT01780675	Jose Belderbos, MD, PhD The Netherlands Cancer Institute	168	Prophylactic Cranial Irradiation vs Hippocampal Avoidance PCI 10 times 2.5 Gy (total 25 Gy)	Neurocognitive decline as primary outcome measure recorded by recall score at 4 months	safety as secondary outcome measure	Recruiting
NCT02906384	Ming Chen, PHD Zhejiang Cancer Hospital Yue Kong Zhejiang Cancer Hospital	154	Prophylactic Cranial Irradiation vs Hippocampal Avoidance PCI 10 times 2.5 Gy (total 25 Gy)	memory preservation responses to Hopkins Verbal Learning Test as primary outcome measure	OS, hippocampus metastasis and image changes of brain as secondary outcome measure	Recruiting
NCT02058056	Francesca Caparrotti, MD Hôpitaux Universitaires de Genève, Genève	42	Irradiation HA-PCI concomitant to the second cycle of CHT and to tRT for patients with LD SCLC	Neurocognitive functioning (NCF) measured by Hopkins Verbal Learning Test Revised (HVLT-R), Controlled Oral Word Association (COWAT) and Trail Making Test Part A and B (TMT A/B)	BMFS, Adverse events, neurotoxicity, individual tests for each cognitive domain, OS and QoL are secondary outcome measures	Completed
NCT02397733	Núria Rodríguez de Dios, MD PhD Hospital de la Esperanza. Department of Radiation Oncology Barcelona, Spain	150	Prophylactic Cranial Irradiation vs Hippocampal Avoidance PCI 10 times 2.5 Gy (total 25 Gy)	Neurocognitive functioning (NCF) (Free and Cued Selective Reminding Test) 3 months after radiation	Neurocognitive functioning (NCF) 6, 12, 24 months after radiation, Hippocampus brain metastases, Hippocampus volume, Adverse effects and QoL are secondary outcome measures	Recruiting
NCT02366741	Leor Zach, MD, Sheba Medical Center, Israel	5	Irradiation (WBRT) with reduced dose to the hippocampi of patients with histologically confirmed LD SCLC and complete response (CR) of the primary lesion after chemo-radiotherapy	measure of feasibility (number of patients that complete neuro-cognitive and clinical follow up after WBRT with HC sparing)	neurocognitive testing, QOL, changes in serum markers for neuronal damage, changes in imaging biomarkers (TRAM) and neurocognitive tests score	unknown